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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,144	09/27/2004	Kurt Berlin	82309	6722

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
11/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,144	BERLIN, KURT	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

/DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/23/2009 has been entered.

Claim Status and formal Matters

Claims 1-15 are pending.

Claims 12-15 are withdrawn.

Claim 1 has been amended.

The previous grounds of rejection have been withdrawn in view of the amendments and upon further consideration.

Priority

The instant application was filed on 9/27/2004 as a National Stage entry of PCT/EP03/03104 filed 3/25/2003 and claims priority to German Application 102 14 232.7 filed 3/25/2003.

Claim Rejections - 35 USC § 103- New Grounds Necessitated by Amendment

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-6, 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berlin et al (WO01/27317, published 4/1/2001) in view of Allis (WO02/18418 published 3/7/2002), Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and New England BioLabs catalog (2000-2001), page 91.

Citations from Berlin et al (WO01/27317, published 4/1/2001) refer to the National Stage (U.S. Patent No. 7,179, 594 issued 2/20/2007). The National Stage is deemed an English language translation of the PCT.

Berlin teaches a method of detecting the methylation state of genomic DNA samples (column 1, lines 27-30). Berlin teaches that in PCR amplification 5-methylcytosine in completely lost (column 1, line 40). Berlin teaches that bisulfite methylation analysis of sample fragments from small samples is not reliable (column 3, lines 47-50). Berlin teaches that methylase enzymes methylate cytosine in a sequence specific manner were known (column 3, lines 46-50). Berlin teaches that samples can be amplified by a cyclic process, such as PCR, prior to the detection of cytosines (column 4, lines 36-40). Berlin teaches that a genomic sample can be methylated by a methyl transferase, prior to chemical treatment and analysis (column 4, lines 10-20). Berlin teaches the use of genomic DNA. Berlin further teaches 5 methyl cytosine is the most common genetic modification in eukaryotic cells (1st column, lines 33-34).

With regards to claim 5, Berlin teaches the DNA can be labeled using one or more detectable nucleotides incorporated during synthesis (column 4, lines 51-55). Thus Berlin teaches a detectable labeled can be synthesized into a CpG island.

With regards to claim 6, Berlin teaches at least one oligomers (primer) is attached to a surface (column 4, lines 62-65).

With regards to claim 8, Berlin teaches a polymerase dependent primer extension reaction is carried out of the surface (column 5, lines 40-45). The polymerase bound to the primer is immobilized on the surface.

With regards to claim 8-9 and 11, Berlin teaches methylation defection by bisulfite treatment (column 2, lines22-51).

With regards to claim 10, Berlin teaches detection of methylation by methylation sensitive restriction digestion (column 1, lines 53-67).

Berlin does not teach contacting a hemimethylated DNA with a methyl transferase and a methyl donor under conditions conducive to methylation of the synthesized strands such that the methylation on the synthesized strands are consistent with the starting genomic sample.

However, Allis teaches, “a mechanism for replicating methylated CpG dinucleotides exists: maintenance DNA methyl transferase (DNMTs) recognize hemimethylated DNA (DNA methylated on only one strand) and add methyl groups to the cytosine residues on the complementary strand." (page 36, lines 20-27).

Pradhan et al teaches the use of DNMT1 as a methyltransferase (see abstract). Pradhan teaches maintenance methylation "ensures propagation of tissue specific methylation patterns during development" (see page 33002, first column text, lines 8-10). Pradhan teaches that DNMT1 has a higher reaction velocity for hemimethylated DNA substrates (see page 3302, 2nd column, last paragraph). Pradhan thus teaches DNMT1 is a maintenance methyltransferase ensures propagation of specific methylation patterns. Pradhan further teaches cytosine methylation is important in embryonic development, carcinogenesis and genetic disease (see page 33002, 1st column of text lines 1-5). Pradhan thus teaches maintenance methylation and the methyltransferases that maintain methylation patterns are important in embryonic development, carcinogenesis and genetic disease. Pradhan teaches the use of DNA known to be methylated (page 33006, 2nd column, last paragraph).

With regards to claim 4, Pradhan teaches the use of S-adenosylmethionine as a methyl donor.

New England BioLabs catalog (page 91) teaches that DNMT1 was known at the time for use in molecular biology methods.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to analyze genomic DNA by amplifying genomic methylated DNA in cycling type amplification method as suggested by the combination of Berlin, Allis, Pradhan and NEB catalog. The artisan would be motivated to overcome the issues of the inability to reliably analyze small fragments and small samples as taught by Berlin by amplifying nucleic acid while maintaining methylation patterns. The

artisan would be motivated to provide a sample, heat a sample in the presence of a primer and nucleotides to allow for synthesis, then added s-adenosylmethionine and DNMT1 to the reaction and repeat before analysis of the methylation status. Berlin teaches the use of a cycling process and the use of PCR which suggests the use of heating and cooling of the reaction mixture and analysis of methylation. Further Berlin, teaches the use of a regular PCR process dilutes the methylation pattern. Allis teaches methods of replicating CpG methylation patterns using DNMT of hemimethylated DNA was known, while Pradhan give specific guidance to the reaction conditions for methylation and the use of s-adenosyl methionine. Thus the artisan would have a reasonable expectation of success combining known heating and cooling cycles for a primer extension reaction with the use of known methyltransferase (DNMT1), which has known reaction conditions.

Response to Arguments

The response asserts that the substitution of DNMT1 in the method of Lopez is totally unsuitable. The art of Lopez is no longer present in the instant rejection and thus these arguments are moot.

The response continues by asserting that one should first focus on the problem being solved to identify the closest prior art. The instant claims are drawn to methods of amplifying nucleic acids in a manner in which methylation is preserved from the genomic DNA is such a way that analysis of the amplified sample would allow for determination of the methylation status of the starting DNA. Berlin teaches that difficulties in the prior art due to small sample size and small fragment analysis, as well

as traditional PCR diluting methylation status. Further Berlin teaches analysis of DNA after amplification and methylation. Berlin does not specifically teach maintenance of methylation, however Allis teaches methylation can be replicated by use of DNMT. Thus combined with the specifics of DNMT1 disclosed by Pradhan, the claims are obvious over the prior art of record.

The response continues by asserting that the method enables analysis of in vivo genomic DNA methylation. This argument has been thoroughly reviewed but is not considered persuasive as the claims are not limited to in vivo methylated DNA, but genomic template DNA. Thus assertion that the method is limited to in vivo methylated DNA is a limitation that is not present in the claims as the claims are broadly drawn to "any' genomic DNA, which could be methylated in vivo or in vitro.

The response continues to argue Lopez, which is no longer present in the rejection and thus these arguments are not considered.

The response than moves to the teachings of Berlin and asserts that the teachings of Berlin clearly refer to DNA which has been pretreated with bisulfite in order to translate sequences changes with methylation. These arguments have been thoroughly reviewed but are not considered persuasive as the claims do not preclude the use of bisulfite treatment as asserted, contrary claim 11 specifically requires bisulfite treatment.

The response continues by asserting on page 14 that Berlin teaches away from methods of analysis based on hybridization such as PCR without performing suitable pretreatment. This arguments have been thoroughly reviewed but is not considered

persuasive as the claims do not exclude the use of hybridization or pretreatment as an analysis step as asserted, but specifically require it in claims 9 and 11.

The response concludes that any method that uses PCR in methylation analysis is not a suitable method for methylation analysis (page 14-top page 15). These arguments have been thoroughly reviewed but are not considered persuasive as the claims do not exclude the use of PCR or bisulfite treatment in any step of the claims. Further this argument appears to be inconsistent with claims 9 and 11.

The response then incorrectly asserts the closest art is amplification based on pre-treatment with bisulfite. This argument has been thoroughly reviewed but is not considered persuasive as Berlin teaches amplification without pretreatment followed by methylation (abstract). The response continues that the differences to the closest prior art is not pre-treated the genomic DNA and instead perform steps A-D and add a methyltransferase then repeat. These arguments have been thoroughly reviewed but are not considered persuasive as they are arguments of counsel that have not been supported by evidence and are contradicted by the teachings of Berlin which suggest amplification without pretreatment. Further the claims as presented do not exclude pretreatment, contrary to the assertion of the response.

The response continues by asserting there is an unexpected result that the polymerase mediated chain reaction would work in the presence of a heat labile methylation sensitive methyltransferase. These arguments have been thoroughly reviewed but are not considered persuasive as they are argument of counsel that has

not been substantiated by evidence. Specifically, there is no evidence that a primer extension in the presence of a methyl transferase is an unexpected result.

The response continues the teachings of Pradhan do suggest the use of DNMT1 in targeting the amplification of small amounts of DNA. These arguments have been thoroughly reviewed but are not considered persuasive as the DNMT1 targets exon 1 for methylation, which is a short target (figure 6). Further New England BioLabs catalog (2000-2001), page 91, clearly indicates the DNMT1 is a known molecular biology enzyme contrary to the assertion of the response. Finally, the claims are not limited to small fragments as asserted and Allis specifically teaches DNMT for replication of methylation.

The response continues by asserting that Pradhan's teachings are limited to disclosing the role of an enzyme and its role in vivo, but does not necessarily what the enzyme does in vitro. These arguments have been thoroughly reviewed but are not considered persuasive as Pradhan assays the activity of the enzyme in vitro and discloses it is more active towards hemimethylated substrates (tables II, III, and IV). Thus these arguments are not persuasive. Further the presence of DNMT1 in the New England Biolabs catalog clearly indicates that it is known to be used in molecular biology methods. Further the teachings of Allis render this limitation even more obvious contrary to the assertion of the response.

The response continues by asserting that Pradhan does not teach the enzyme is heat resistant or stable in conditions for PCR. These arguments have been thoroughly reviewed but are not considered persuasive as the claims nor rejection require the

enzyme is stable in PCR conditions or are heat stable. Thus these arguments are beyond the scope of the claimed invention.

The response then again presents arguments to the closest prior art, which are not persuasive for the reasons previously presented.

The response then asserts there is no reason to select the enzyme and replace the bisulfite method of Berlin with a new and potentially unreliable enzymatic treatment. these arguments have been thoroughly reviewed but are not considered persuasive as discussed above the response has mischaracterized the teachings of Berlin, by asserting Berlin only teaches amplification following bisulfite treatment. Further the response has again asserted that the claims are limited to nucleic acids that have not been pretreated, when the claims require DNA or perhaps genomic DNA.

The response concludes by asserting that nowhere is it suggested that amplification of genomic DNA in order to replicate methylation pattern is suggested. These arguments have been thoroughly reviewed but are not considered persuasive as the Allis clearly suggest replication of methylation, which would render amplification obvious based on the teachings of cited art.

4. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berlin et al (WO01/27317, published 4/1/2001) in view of Allis (WO02/18418 published 3/7/2002), Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010), and New England BioLabs catalog (2000-2001), page 91 as applied to claims 1-6, and 8-11 above, and further in view of Shatkin et al (US Patent 6312926).

The teachings of Berlin, Allis, Pradhan, and NEB catalog are set forth above. Berlin, Allis and Pradhan do not teach the methyltransferase immobilized on a solid support.

However, Shatkin et al teaches the use of hMET (methyl transferase) immobilized on protein G beads for washing assays (see column 24, lines 3-12).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to Berlin, Allis, Pradhan, and NEB catalog method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase taught by Shatkin, because Shatkin teaches immobilization allows washing of assays. The ordinary artisan would be motivated to improve Berlin, Allis, Pradhan, and NEB catalog method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase or polymerases as taught by Shatkin, because Shatkin teaches immobilization allows washing of assay and detection of protein interactions.

Response to Arguments

The response of asserts that Shatkin et al does not cure all of the deficiencies of Berlin, Allis, Pradhan, and NEB catalog , as previously presented in the response. These arguments have been thoroughly reviewed but are not considered persuasive because as discussed above Berlin, Allis, Pradhan, and NEB catalog do render the instant claims obvious as the combination would result in a method of amplifying genomic DNA wherein the methylation status of the genomic DNA is maintained. The

response does not set forth any other arguments to this rejection, thus this rejection is maintained.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-5 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-12 and 15 of copending Application No. 11/904,320 in view of Allis (WO02/18418 published 3/7/2002) and Berlin et al (WO01/27317, published 4/1/2001).

This is a provisional obviousness-type double patenting rejection.

Instant claims 1-5 are drawn to a method of cytosine methylation analysis by providing a template DNA, heating the template DNA, cooling the template DNA in the presence of primers, heating the DNA in the presence of a polymerase, contacting the hemimethyalted DNA in the presence of a methyl transferase and a methyl done to

result in the methylation of the corresponding CpG and repeating the steps a plurality of time before analyzing the sample. Claim 11 of '320 is drawn to converting a genomic DNA by a copying reaction (primer extension of pending claims), treating the sample with a methyl transferase specific for hemimethylated DNA using s-adenosylmethionine and detecting the presence of the s-adenosyl methionine. Claim 12 of '320 is draw generating a hemimethyalted double stranded DNA by heating and annealing DNA samples, labeling hemimethylated double stranded using DNMT1 and a labeled s-adenosylmethionine and analyzing the sample.

The claims of '320 do not specifically teach or suggest repeating the steps.

However, Allis teaches, "a mechanism for replicating methylated CpG dinucleotides exists: maintenance DNA methyl transferase (DNMTs) recognize hemimethylated DNA (DNA methylated on only one strand) and add methyl groups to the cytosine residues on the complementary strand." (page 36, lines 20-27).

Berlin teaches that bisulfite methylation analysis of sample fragments from small samples is not reliable (column 3, lines 47-50). Berlin teaches that samples can be amplified by a cyclic process, such as PCR, prior to the detection of cytosines (column 4, lines 36-40).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to repeat the process of the claims of '320 to produce a plurality of nucleic acids to allow sufficient quantities to improve reliability of the assays as taught by Berlin in view of the teachings of Allis and Berlin. The artisan

would have a reasonable expectation of success as the artisan is using known methods in a manner suggested by the art.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Examiner, Art Unit 1634

Steven Pohnert